1. NAME OF THE MEDICINAL PRODUCT

Dropivit 20.000 IE/ml druppels voor oraal gebruik, oplossing

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution (40 drops) contains 0.5 mg cholecalciferol, which is equivalent to 20 000 IU vitamin D_3.

1 drop is equivalent to 500 IU vitamin D_3.

See Section 6.1 for the full list of excipients.

3. PHARMACEUTICAL FORM

Oral drops, solution
Transparent, slightly yellowish, viscous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Initial treatment of vitamin D deficiency (serum 25(OH)D < 25 nmol/l) in adults and adolescents.
- Prevention of vitamin D deficiency in adults and adolescents with an identified risk.
- As an adjunct to specific therapy for osteoporosis in adult patients with vitamin D deficiency or at risk of vitamin D deficiency.

4.2 Posology and method of administration

Posology

The dosage must be determined individually by the treating doctor, depending on the extent of the necessary vitamin D3 supplementation.

Adults

Initial treatment of vitamin D deficiency (serum 25(OH)D < 25 nmol/l):

Recommended dose: 1000 IU (2 drops) to 4000 IU (8 drops) per day.

After the first month, a lower maintenance dose should be considered according to the desirable serum levels of 25-hydroxycholecalciferol (25 (OH) D), the severity of the disease and the patient's response to treatment. A suitable maintenance dose could be 1000 IU (2 drops) per day.

Prevention of vitamin D deficiency in adults with an identified risk:

Recommended dose: 500 IU (1 drop) to 1000 IU (2 drops) per day

As an adjunct to specific therapy for osteoporosis in patients with vitamin D deficiency or at risk of vitamin D deficiency:

Recommended dose: 1000 IU (2 drops) per day.

Hepatic impairment
No dosage adjustment is required in patients with hepatic impairment.

Renal impairment
In severe renal impairment the dosage must be determined individually by the treating physician dependent upon desirable serum levels of 25-hydroxycholecalciferol (25(OH)D), the severity of the disease and the patient´s response to treatment (see section 4.4).

Paediatric population

Children <12 years of age
<Product name> is not recommended in children under 12 years of age.

Adolescents

Initial treatment of vitamin D deficiency (serum 25(OH)D < 25 nmol/l):

Recommended dose: 1000 IU (2 drops) per day.

Prevention of vitamin D deficiency in adolescents with an identified risk:

Recommended dose: 500 IU (1 drop) to 1000 IU (2 drops) per day.

Method of administration

<invented name> 20 000 IU/ml oral drops, solution should be taken in a spoonful of liquid.

The bottle containing the product must be held upside down, in a vertical position. It may take some time for the first drop to appear.

<invented name> 20 000 IU/ml oral drops, solution may be taken independently of meals.

4.3 Contraindications

- Hypersensitivity to the active ingredient of the medicinal product or to any of its excipients listed in Section 6.1.
- Diseases and/or conditions accompanied by hypercalcemia and/or hypercalciuria.
- Calcium-containing kidney stones, nephrocalcinosis.
- Hypervitaminosis D.

4.4 Special warnings and precautions for use

Monitoring
During initial and long-term treatment, serum calcium levels should be followed and renal function should be monitored through measurements of serum creatinine. Monitoring is particularly important in elderly patients who concurrently take cardiac glycosides or diuretics (see section 4.5) and in patients with a high tendency to calculus formation. In case of hypercalcemia or if symptoms of renal impairment occur, the dose must be lowered, or the treatment must be discontinued.

Renal impairment
Cholecalciferol should be used with caution in patients with renal impairment and the effect on calcium and phosphate levels should be monitored. The risk of soft tissue calcification should be taken into account. In patients with severe renal impairment, vitamin D in the form of cholecalciferol is not metabolised normally (see section 4.2).

Sarcoidosis

Vitamin D_3 may only be administered with caution to patients with sarcoidosis, due to the risk of increased conversion of vitamin D into its active form. In these patients, blood and urine calcium levels must also be monitored regularly.

Other vitamin D_3 containing products
The dose of vitamin D in this medicinal product should be considered when taking other medicinal products containing vitamin D. Additional doses of vitamin D should be taken under close medical supervision.

Pseudohypoparathyroidism
Vitamin D should not be taken if pseudohypoparathyroidism is present (the need for vitamin D may be reduced by the sometimes normal sensitivity to vitamin D, with a risk of long-term overdose). In such cases, more manageable vitamin D derivatives are available.

4.5 Interaction with other medicinal products and other forms of interaction

Thiazide diuretics
Thiazide diuretics reduce the excretion of calcium in the urine. Due to the increased risk of hypercalcemia, serum calcium should be regularly monitored during concomitant use of thiazide diuretics.

Corticosteroids
Systemically administered corticosteroids prevent the absorption of calcium. Long-term administration of corticosteroids may counteract the effect of vitamin D.

Ion-exchange resins and laxatives
Ion-exchange resins (such as cholestyramine, colestipol) or laxatives (such as paraffin oil) may decrease the absorption of vitamin D.

Orlistat
Orlistat treatment may reduce the absorption of liposoluble vitamins, including vitamin D.

Magnesium
In the case of concomitant administration of magnesium-containing medicinal products (such as antacids) and vitamin D, the monitoring of serum magnesium levels may possibly be required.

Digitalis and other cardiac glycosides
Hypercalcemia developing during vitamin D treatment may increase the toxicity of cardiac glycosides. Concurrent administration of calcium combined with vitamin D_3 requires ECG monitoring and regular checking of serum calcium levels.

Phenytoin or barbiturates
Concomitant use of phenytoin or barbiturates may reduce the effect of vitamin D since the metabolism increases.

Phosphorus-containing products
Concurrent administration of high doses of phosphorus-containing products may increase the risk of hyperphosphatemia.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are limited data from the use of cholecalciferol in pregnant women. Vitamin D deficiency is harmful for mother and child. High doses of vitamin D have been shown to have teratogenic effects in animal experiments (see section 5.3).

Overdose of vitamin D must be avoided during pregnancy, as prolonged hypercalcemia may lead to physical and mental retardation, supravalvular aortic stenosis and retinopathy of the child.

Where there is a vitamin D deficiency the recommended dose is dependent on national guidelines, however, the maximum recommended dose during pregnancy is 4 000 IU/day vitamin D3. For treatment with <invented name> during pregnancy this maximum dose 4 000 IU/day vitamin D3 (8 drops in total) should not be exceeded.

Breast-feeding
Vitamin D3 and its metabolites are excreted in breast milk. No adverse events have been observed in infants. <invented name> can be used at recommended doses during lactation in case of a vitamin D deficiency. This should be considered when giving additional vitamin D to the child.

Fertility
There are no data on the effect of cholecalciferol on fertility. However, normal endogenous levels of vitamin D are not expected to have any adverse reactions on fertility.

4.7 Effects on ability to drive and use machines

<Invented name> has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Adverse reactions (side effects) are listed below by system organ class and frequency. Frequencies are defined as follows: very common (≥1/10); common (≥1/100 – <1/10); uncommon (≥1/1000 – <1/100); rare (≥1/10 000 – <1/1000); very rare (<1/10 000); not known (the frequency cannot be estimated from the available data).

Immune system disorders
Not known (cannot be estimated from the available data): hypersensitivity reactions such as angio-oedema or laryngeal oedema.

Gastrointestinal disorders
Not known: constipation, flatulence, nausea, abdominal pain, diarrhea

Skin and subcutaneous disorders
Rare: pruritus, rash and urticaria.

Hypercalcaemia
Uncommon: Depending on the dose and duration of treatment, severe and prolonged hypercalcemia with its acute (cardiac arrhythmias, nausea, vomiting, psychic symptoms, disturbances of consciousness) and chronic (increased urgency to urinate, increased thirst, loss of appetite, weight loss, kidney stones, kidney calcification, calcification in tissues outside the skeleton) consequences can occur. A fatal outcome has been reported in very rare cases (see also section 4.4 and 4.9).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Overdose of the medicinal product may cause hypervitaminosis and hypercalcemia. Symptoms of hypercalcemia: anorexia, nausea, vomiting, constipation, abdominal pain, muscle weakness, tiredness, confusion, polydipsia, polyuria, dehydration, bone pain, calcification in the kidneys, formation of kidney stones, and in severe cases arrhythmia. In extreme cases hypercalcemia may lead to coma or

death. Permanently high calcium levels may cause irreversible renal impairment and soft tissue calcification.

Management of hypercalcemia: vitamin D (and calcium) treatment must be discontinued. At the same time, in such cases the administration of thiazide diuretics, lithium, vitamin A and cardiac glycosides must also be suspended. In patients with reduced level of consciousness, the stomach must also be emptied. Rehydration and – depending on the degree of severity of the overdose – monotherapy or combination treatment may be administered with loop diuretics, bisphosphonates, calcitonin and corticosteroids. Serum electrolytes, renal function and urine output must be monitored. In severe cases ECG and central venous pressure monitoring is also required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic classification: vitamin D and its analogues, cholecalciferol
ATC code: A11CC05

Mechanism of action
Cholecalciferol (vitamin D3) is formed in the skin on exposure to UVB light and converted into its biologically active form, 1,25-dihydroxycholecalciferol, in two hydroxylation steps, first in the liver (position 25) and then in the renal tissue (position 1).

In its biologically active form, vitamin D_3 stimulates calcium absorption, the incorporation of calcium into the osteoid and the release of calcium from the bone tissue. In the small intestine, it promotes rapid and delayed absorption of calcium. The passive and active transport of phosphate is also stimulated. In the kidney, it inhibits the excretion of calcium and phosphate by promoting tubular reabsorption. The formation of parathyroid hormone (PTH) in the parathyroid glands is directly inhibited by the biologically active form of vitamin D_3. PTH secretion is also inhibited by increased calcium absorption in the small intestine under the influence of biologically active vitamin D_3.

5.2 Pharmacokinetic properties

Absorption
Vitamin D_3, which is liposoluble, is absorbed from the small intestine in the presence of bile acids, by means of micelles, and then gets into the blood stream via the lymphatic circulation. It is more readily absorbed from water-soluble polar forms (25(OH)-D), but these are present only in specific parts of food (such as meat, milk).

Distribution and biotransformation
Cholecalciferol and its metabolites circulate in the blood bound to a specific globulin. Cholecalciferol is hydroxylated in the liver to 25-hydroxycholecalciferol (25(OH)-D), which is converted into active 1,25-dihydroxycholecalciferol ($1,25(OH)_2$-D) in the kidneys. The 1,25-dihydroxycholecalciferol metabolite is responsible for the increase of calcium absorption. Non-metabolized vitamin D is stored in adipose and muscle tissue. Elimination is slow: plasma half-life of vitamin D ranges between 15 and 25 hours. However, liposoluble vitamin D can be detected in stored form in the tissues for as long as several months: accordingly, the biological elimination half-life is almost 2 months.

Elimination
Vitamin D is excreted in the bile and eliminated in the feces. Some of its water-soluble metabolites are also partly excreted in the urine.

5.3 Preclinical safety data

At doses far higher than the human therapeutic range teratogenicity has been observed in animal studies. No other relevant data is available that has not been mentioned elsewhere in the SmPC (see section 4.6 and 4.9).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Triglycerides, medium chain.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.
Store in the original package in order to protect from light.

6.5 Nature and contents of container

10 ml solution filled into type III brown glass bottle closed with HDPE screw cap fitted with LDPE dropper, placed into cardboard box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

METEOR Trade Kft.
Rigó Utca 1
4030 Debrecen
Hongarije

8. MARKETING AUTHORIZATION NUMBER(S)

RVG 130323

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Datum van eerste verlening van de vergunning: 11 maart 2024

10. DATE OF REVISION OF THE TEXT